Surgical decision-making for long bone metastases

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CHAPTER 13

General Discussion

The introduction of this PhD thesis describes the unique features of managing bone lesions secondary to metastasis. Numerous aspects that need to be considered when deciding upon a surgical strategy have been addressed in the previous chapters. Specific study aims concerning surgical management of bone metastasis were divided into three main parts; metastatic femoral lesions, metastatic humeral lesions, and survival.

PART I: METASTATIC FEMORAL LESIONS

The proximal femur is the most commonly affected long bone by metastasis. Breast, lung, prostate, and renal cell cancer are the most common bone metastases in the femur, and together account for 68% of all femoral metastases.[1] General consensus is that surgical treatment is indicated in case of a pathological fracture or when a fracture is impending and the estimated life expectancy exceeds the recovery time.

Several surgical options to treat metastatic lesions of the proximal femur exist –and are often categorized into endoprosthetic reconstruction, intramedullary nailing, and open reduction internal fixation with plate and screws–. There is substantial controversy among orthopaedic oncologists about when which surgical strategy is recommended.[2] This is attributed to the low level of evidence with inherent biases and potential for confounding, small sample sizes lacking statistical power, and lack of studies measuring patient reported outcomes. We found –in our relatively large (n = 417) retrospective cohort of patients that underwent surgery for proximal femoral metastasis (excluding the femoral head)– no difference in overall reoperation rate between endoprosthetic reconstruction, intramedullary nailing, and open reduction internal fixation (Chapter 2). However, when focusing on specific reasons for reoperation, we found that fixation failure most commonly occurred after open reduction internal fixation (13% versus 3.0% after intramedullary nailing versus 0% after endoprosthetic reconstruction), whereas deep infection was most common after endoprosthetic reconstruction (8.6% versus 2.0% after intramedullary nailing versus 0% after open reduction and internal fixation). Systemic complication rate and 30-day mortality did not differ between surgical strategies. Intraoperative blood loss was almost twice as high and anesthesia time was about 40 minutes longer for endoprosthetic reconstruction when compared with intramedullary nailing and open reduction internal fixation. Our additional study finding that a worse prognostic survival score (i.e. a lower modified Bauer score [a score that combines cancer type and degree of dissemination]) is associated with a higher risk of systemic complications could be used to anticipate postoperative problems, and identify patients that might benefit from preoperative optimization. The overall reoperation rate in our study (7.2%) is consistent with reoperation rates reported in the two largest previous studies that directly compared all three surgical strategies by Steensma et al. (6.4%)[3] and Wedin et al. (10%)[4]. Our results are also consistent with these two previous studies in terms of durability of endoprosthetic reconstructions (i.e. low fixation failure rates): Steensma et al.[3] found that 0.5% of endoprosthetic reconstructions required implant exchange after fixation failure compared to 6.1% after intramedullary nailing and 42% after open reduction internal fixation. Wedin et al.[4] demonstrated an 8.3% fixation failure rate requiring reoperation after endoprosthetic reconstruction compared with 13% after intramedullary nailing and 25% after the use of a dynamic hip screw. This cohort study is followed by our systematic review of the literature (Chapter 3) in which we demonstrated that the overall reoperation rate was highest after open reduction internal fixation (14%), and comparable for intramedullary nailing (4.2%) and endoprosthetic reconstruction (5.2%). Separating reasons for reoperation, we again identified that the fixation failure rate was highest after open reduction internal fixation (10%), followed by intramedullary nailing (2.8%), and endoprosthetic reconstruction (0.4%); whereas, deep infection rate was highest after endoprosthetic reconstruction (0.68%) as compared to intramedullary nailing (0.04%) and open reduction internal fixation (0.00%). Systemic complications were inconsistently reported among studies and therefore not comparable. Patient reported outcomes such as function and pain were scarcely reported according to our systematic review and we therefore could not draw any conclusions on these outcomes. Findings from our retrospective cohort study and systematic review suggest that extramedullary fixation in the form of open reduction internal fixation with plate and/or screws or a dynamic hip screw is an inferior option for treatment of metastatic proximal femoral lesions unless the medullary canal is not accessible (e.g. due to already present implants or osteoblastic intramedullary tumor depositions). Endoprosthetic reconstruction and intramedullary nailing seem to be comparable in terms of overall reoperation rate; however endoprosthetic reconstructions more commonly develop deep infections (often an early complication), whereas intramedullary nail fixation seems to fail more often over time (often a late complication). These implant-specific reasons for reoperation as well as their timing should be considered when deciding between endoprosthetic reconstruction and intramedullary nailing. We therefore argue that life expectancy is an important factor for establishing which surgical strategy is most optimal for proximal femoral metastases. Future study on the impact of these local complications (deep infection and fixation failure) on recovery and functional outcome would be valuable.[5] The difference in surgical time and blood loss, and no difference in systemic complications and 30-day mortality does, in general, not influence our recommendation for a surgical strategy. Our findings can be used to inform future patients and caregivers. The most important limitations of the systematic literature review are that all studies were retrospective cohort studies and indications for surgical strategies as well as definition of outcomes to be reported varied among studies or were not clearly described which could have lead to bias. Future studies need to: use standardized methods of reporting by adhering to guidelines to improve study quality (e.g. STROBE guidelines)[6], report definitions of complications including timing and treatment consequences to allow comparison across studies[7], and incorporate patient reported outcome measures to better establish the impact of treatment modalities on patients function and quality of life.[8,9] Furthermore, multi-institutional collaboration by sharing databases are needed to obtain large patient samples as adverse outcomes such as reoperations are relatively uncommon and analyses often lack sufficient power to detect differences. A multi-center prospective randomized controlled trial comparing long-stem cemented hemiarthroplasty with intramedullary nailing for proximal femoral metastases is ongoing and aims to further determine which treatment is optimal in terms of quality of life and physical function.[10] In addition, it would be valuable to understand the rapidity of postoperative recovery in terms of improvement of quality of life and physical function over time in order to determine the minimal estimated life expectancy that justifies surgical intervention. Based on our retrospective cohort study and systematic review, a treatment scheme to guide surgical decision making for proximal femoral metastasis is proposed (Figure 1).

Many studies underline the importance of incorporating functional outcome measures; however, only few attempted to do so as can be concluded from our systematic reviews.[1,11] Some studies use the clinician reported Musculoskeletal Tumor Society (MSTS) score –six items evaluating function through the eyes of the clinician–; however, doctors consistently overestimate a patients' function and mental health. This discrepancy can lead to: less satisfaction among patients as their expectations are not met or their recovery is slower than expected, patients might feel misunderstood or unheard by their physician which could in turn lead to less compliance with treatment recommendations, distorted study results when physicians evaluate the outcome of certain treatments towards they are biased, an attitude of complacency and inertia among clinicians that precludes further improvement, and finally third-party payers that may use reported (overestimated) outcomes to dissuade further innovation and research.[12-15] Use of clinician reported outcomes should therefore be discouraged and obtaining patient reported outcome measures is important.[15-18] We assessed which patient reported outcome measure is most useful –efficient, reliable, and covers the full spectrum of functional levels– to measure physical function among patients with lower extremity metastases (Chapter 4). We approached 115 patients with lower extremity metastases from two orthopaedic oncology clinics to participate in this study. One hundred patients completed five questionnaires and we found that the PROMIS Physical Function, the Toronto Extremity Salvage Score, and the Lower Extremity Function Score had good coverage and high reliability over a wide range of functioning; however, the PROMIS Physical Function questionnaire is quickest to complete and therefore deemed the most useful. The high rate of participation (100 out of 115 invited patients) indicates that patients with bone metastases are open for participation in patient reported outcome studies despite their relatively poor prognosis. PROMIS questionnaires (Patient-Reported Outcomes Measurement Information System) are developed standardized item banks to measure physical, mental, and social health and is funded by the National Institute of

Health. PROMIS questionnaires allow for Computer Adaptive Testing (CAT) –a dynamic selection of items wherein the response to each item guides the system's choice of the next item– resulting in a tailored series of questionnaires reducing questionnaire burden, while maintaining precision and limiting floor and ceiling effect. Most PROMIS questionnaires are currently only available in English language, but efforts to translate and standardize item banks for use in other countries are undertaken.

The accuracy of establishing if a fracture is impending –i.e. predicting occurrence of a pathological fracture– using historical radiographic measures (e.g. >50% circumferential cortical destruction, defect size >30mm), symptoms (e.g. pain on weight bearing), or a combination thereof (e.g. Mirels[19] score) are not sufficiently accurate.[19-21] New techniques such as finite element analysis and CT-based rigidity analysis have been developed to better predict fracture occurrence; however, these methods are complex and relatively labor intensive.[22-28] We found that our newly developed algorithm –using attenuation coefficients (Hounsfield units) in clinically obtained CT-scans; a simplification of the CT-based rigidity analysis as described by Snyder et al.[24-27]– can predict occurrence of a pathological fracture when focusing on cortical bone only (Chapter 5). Our CT-based calculations did not differ when including all tissue (i.e. trabecular bone, cortical bone, and tumor tissue). This could be explained by the fact that cortical bone contributes more to the load bearing capacity than trabecular bone and tumor tissue.[29] However, the accuracy of our method is only moderate and comparable to radiographic measurements and symptoms. A more controlled study design (prospective followup of patients) with standardized CT-scan protocols might improve the accuracy of our method and merits further study. On the other hand, accurately predicting pathological fracture risk based on a CT-scan only might simply be impossible due to the multitude of other factors that might contribute to pathological fracture occurrence, such as: tumor growth/activity, response to systemic therapy or radiation therapy, activity of the patient, risk of falling, etc. Future studies might test the influence of such factors and study if a combination of lesion characteristics (based on CT imaging) and clinical factors might improve prediction accuracy. More precise determination of fracture risk would reduce the potential for over- and undertreatment of non-fractured metastatic lesions.

PART II: METASTATIC HUMERAL LESIONS

After the axial skeleton and proximal femur, the humerus is the third most commonly affected bone by metastatic cancer. Breast, myeloma, lung, and renal cell cancer are the most common bone metastases in the humerus, and together account for 73% of all humeral metastases.[11] As with femoral metastases, surgical fixation is indicated in case of a pathological fracture or when a fracture seems to be impending; However, the threshold

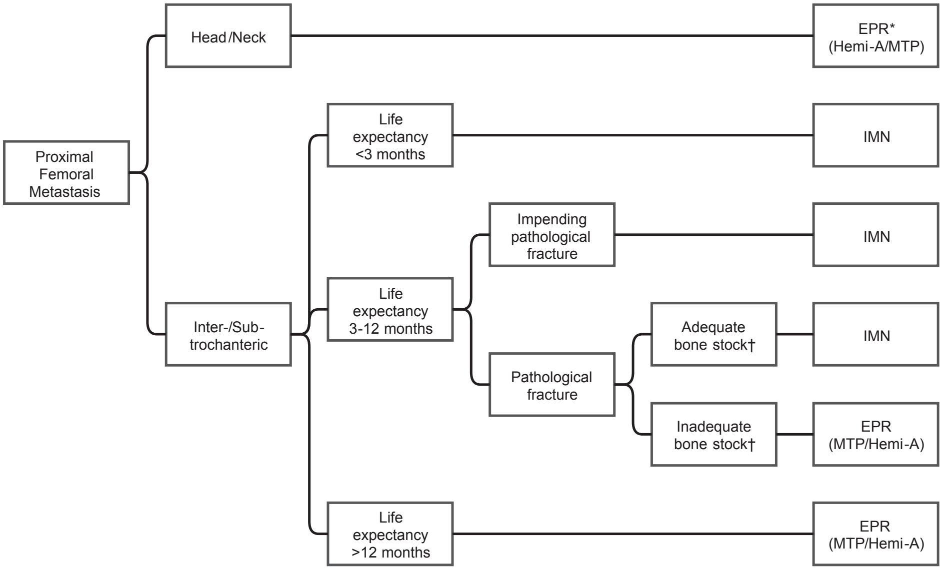

Figure 1: Surgical treatment algorithm for metastatic lesions of the proximal femur.

EPR = Endoprosthetic reconstruction, IMN = Intramedullary nailing, MTP = Modular Tumor Prosthesis, Hemi-A = Hemi-arthroplasty.

*For head/neck lesions and lesions that minimally affect the trochanteric region, a cemented hemi-arthroplasty is the first choice; however, in case of tumor involvement of the trochanteric region, a modular tumor prosthesis is most likely needed to reconstruct the defect.

†Bone stock: adequate bone stock means a small solitary lesion in otherwise healthy bone, inadequate bone stock means multiple lesions and/or diffusely weakened bone.

Extramedullary fixation in the form of open reduction internal fixation with plate and/or screws or a dynamic hip screw is generally not recommended for metastatic proximal femoral lesions unless the medullary canal is not accessible (e.g. due to already present implants or osteoblastic intramedullary tumor depositions).

The entire bone needs to be imaged at least in two directions preoperatively to evaluate for additional metastatic lesions. The implant needs to span at least all metastatic lesions.

This algorithm does not pertain to concomitant metastatic involvement of the acetabular region, it also does not include nonoperative management of for example metastatic lesions of the proximal femoral region that are not at risk of fracture or patients with a life expectancy considered to poor to undergo surgery.

for surgery of a non-fractured metastatic lesion in a non-load bearing bone (such as the humerus) is higher as compared to load bearing bones (e.g. the proximal femur).

Surgical options for treating metastasis to the humerus can be divided into: intramedullary nailing, open reduction internal fixation with plate and screws, and endoprosthetic reconstruction of the proximal, shaft (diaphyseal/intercalary), distal (total elbow), or complete humerus. Our systematic review narratively reports outcomes after these treatment modalities without performing a meta-analysis as indications for surgical strategies vary widely, definition of outcomes vary substantially, and studies are heterogeneous (Chapter 6). None of the included studies described patient reported outcomes, only five studies demonstrated functional outcome as determined by the clinician. We found that intramedullary nailing, plate-screw fixation, and proximal endoprosthetic reconstruction seem to result in reasonable to good function on average. Overall reoperation rates were 4.4% after intramedullary nailing (range: 0 to 10%), 9.3% after plate-screw fixation (range: 5 to 14%), 2.5% after proximal endoprosthetic reconstruction (range: 0 to 6%), and 15% after diaphysis prosthesis (range: 14 to 16%). Although indications for these treatment modalities vary, intramedullary nailing, plate-screw fixation, and diaphyseal prosthesis were all predominantly used for diaphyseal pathological fractures; the diaphysis prosthesis seems to have the highest risk of reoperation due to failure of fixation and peri-implant fracture. This finding might be affected by confounding (e.g. diaphysis prosthesis might be used in larger defects, and/or in patients with better prognosis).[30,31] Intercalary diaphyseal prosthesis should probably be reserved for substantial diaphyseal segmental bone destruction that cannot be easily spanned with a plate-screw construct or intramedullary nail combined with cement augmentation or structural bone grafting in a patient with an otherwise relatively good life expectancy (e.g. in case of a solitary metastasis).[32,33] Methodological quality of future studies should be improved by using standardized methods of reporting (e.g. STROBE guidelines)[6] and by reporting definitions of complications including timing and treatment consequences.[7] In addition, it would be valuable to study patient reported outcome measures to better establish the impact of surgical treatment on patients function and quality of life. Furthermore, multi-institutional collaborations by sharing databases are needed to obtain sufficiently large samples to compare adverse outcomes such as reoperation in relatively homogenous populations (i.e. per anatomical area).

To better understand why implants for metastatic humeral lesions undergo reoperation and why patients develop postoperative complications, we studied a relatively large (n = 295) retrospective cohort of patients that underwent intramedullary nailing, open reduction internal fixation with plate and screws, and proximal endoprosthetic reconstruction of a metastatic humeral lesion (Chapter 7). We found that 8.5% underwent reoperation, predominantly for deep infection (2.0%), nonunion (2.0%), tumor recurrence (1.6%), and peri-implant fracture (1.4%). None of the clinical, tumor, or treatment characteristics were associated with risk of reoperation, except for duration of survival: the risk of reoperation increases from 2.6% at one month up to 19% at two years. This emphasizes the importance of incorporating life expectancy in surgical decision making and underlines the need for durable constructs in patients who are expected to live longer than one year. Based on our systematic review and this retrospective cohort study we cannot determine which implant is most durable; However, complete resection of tumor and reconstruction, or stable fixation combined with radiation of a radiosensitive tumor is probably the most durable in terms of fixation failure. Yet, the evidence supporting radiation therapy to improve local tumor control after surgical fixation for long bone metastasis is limited.[34] Our finding that none of the other factors were associated with reoperation might be explained by the variation in reasons for reoperation (e.g. infection, peri-implant fracture, nonunion etc.) which might have other underlying causes and corresponding risk factors. Our cohort was not large enough to assess risk factors for specific local complications leading to reoperation. Systemic complications occurred in 5.8% of the patients and the modified Bauer score, as with our proximal femoral metastasis study, is the only factor associated with developing postoperative complications. This score facilitates risk stratification and might help identify patients at unacceptable high risk for postoperative complications and patients that might benefit from preoperative optimization.

Evidence supports the use of intramedullary nailing, open reduction internal fixation, and endoprosthetic reconstructions for metastatic humeral lesions.[11] We therefore explored when surgeons (n = 161) used which implant in a cross sectional survey study to improve our understanding of surgical decision making and explore areas of controversy (Chapter 8). Orthopaedic oncologists are more likely to choose plate-screw fixation or endoprosthetic reconstruction, and less likely to choose intramedullary nailing when compared to orthopaedic surgeons not daily involved in skeletal oncological surgery (predominantly trauma surgeons). Recommendation for nonoperative management does not differ between groups. This difference in preference for implants probably has it roots in the difference in training as orthopaedic oncologists are trained in treatment of bone and soft tissue neoplasms, developmental dysplasias, tumor-like conditions, and major skeletal defects.[35] As such, they might be more comfortable with creating bony defects by resection and subsequent reconstruction with a prosthesis or plate-screw fixation with cement augmentation and therefore base their decision for an implant on its combination with adjuvant treatment. It is therefore valuable to discuss metastatic humeral fracture cases preoperatively in a team with an orthopaedic oncologist, medical oncologist, and radiation oncologist. In addition to subspecialty training, we found that: tumor type, estimated life expectancy and anatomical location influenced the recommendation for treatment, while fracture type did not. Nonoperative management was recommended for slightly over one-third of patients with an estimated life expectancy less than 3 months, while surgical management was recommended for almost all patients with a life expectancy over 3 months. Accurate prognostication is important and requires further study as life expectancy is –as our findings demonstrate– an important factor in deciding whether to operate or not. The recommendation for a specific implant was strongly influenced by anatomical location of the lesion: intramedullary nailing (68%) was predominantly recommended for diaphyseal lesions, followed by plate-screw fixation (15%); while all three techniques were recommended for proximal humeral lesions (intramedullary nailing: 38%, endoprosthetic reconstruction: 14%, and plate-screw fixation: 24%). Future studies that directly compare these techniques –preferably in an experimental study design– per anatomical area (Diaphyseal lesions: intramedullary nail versus plate-screw construct. Proximal lesions: endoprosthesis versus plate-screw construct versus intramedullary nail) are needed to elucidate which implant is most optimal in which situation.

Based on these studies, a treatment scheme to guide surgical decision making for humeral metastasis is proposed; however, scientific equipoise results in a large variety of valid options (Figure 2).

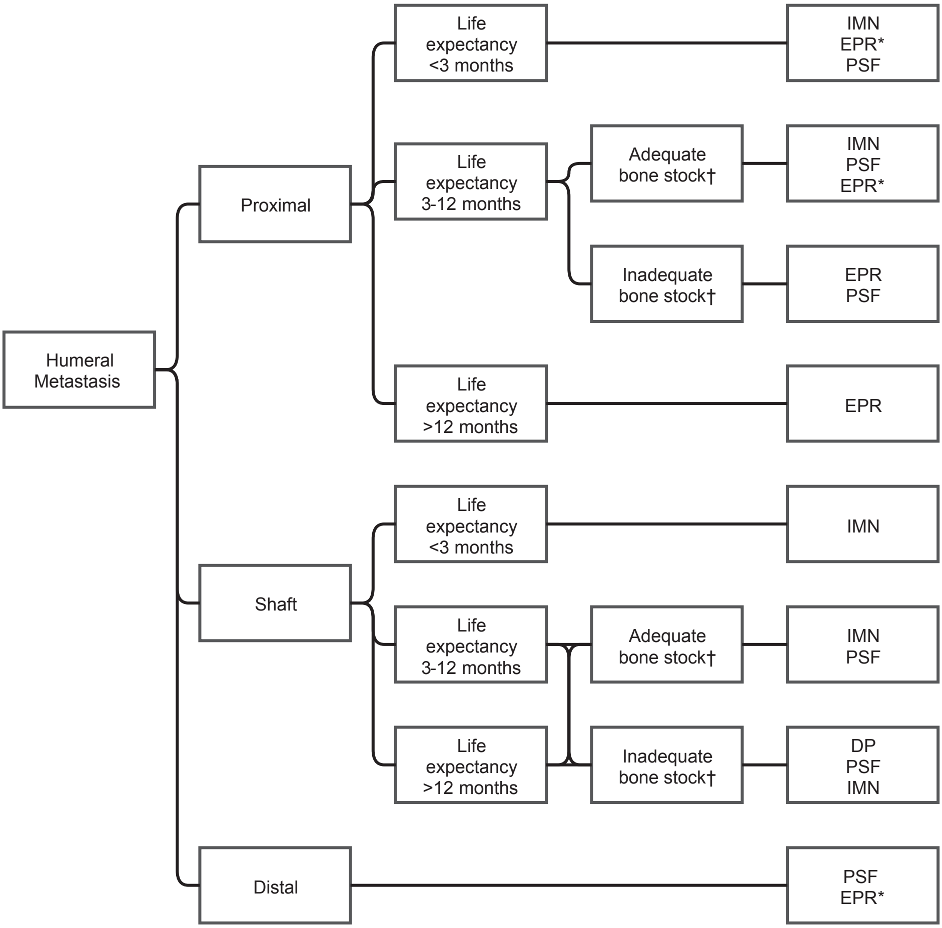

Figure 2: Surgical treatment algorithm for metastatic lesions of the humerus.
EPR = Endoprosthetic reconstruction (proximal or distal), IMN = Intramedullary nailing, PSF = Plate-screw fixation, DP = diaphysis prosthesis.
*Endoprosthetic reconstruction is recommended in case of articular involvement.
†Bone stock: adequate bone stock means a small solitary lesion in otherwise healthy bone, inadequate bone stock means multiple lesions and/or diffusely weakened bone.
The entire bone needs to be imaged at least in two directions preoperatively to evaluate for additional metastatic lesions. The implant needs to span at least all metastatic lesions.
This algorithm does not include nonoperative management of for example metastatic lesions that are not at risk of fracture or patients with a life expectancy considered to poor to undergo surgery.

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PART III: SURVIVAL

Survival of patients with bone metastases that require surgical treatment is generally poor as more than half of the patients decease within one year.[1,11] Life expectancy is considered a key parameter in deciding upon treatment as surgeons need to balance life expectancy against rehabilitation time, longevity of different implants, and risk of tumor recurrence. Treatment of bone metastases is often considered palliative, aiming to providing pain relief and optimize quality of life. However, some previous studies suggest that surgical management of bone metastases could improve survival in specific populations.[36-38]

Patients with bone metastasis from renal cell carcinoma have a relatively favorable prognosis and some studies suggest improved survival after metastasectomy (i.e. en bloc resection) versus intralesional treatment in patients with a solitary metastasis.[36-38] We therefore assessed difference in local tumor recurrence/progression, reoperation, and survival based on type of resection and margin status in patients (n = 183) undergoing surgery for bone metastasis from renal cell carcinoma (Chapter 9). Our retrospective study demonstrates that the risk of developing local recurrence is higher among patients who undergo intralesional curettage and stabilization only as compared to patients who undergo metastasectomy; and that negative margins results in the lowest risk of local recurrence. Two previous studies support this finding of higher local recurrence rate after intralesional procedures compared with wide resection.[39,40] Residual tumor after intralesional treatment most likely explains this higher risk of local recurrence as compared to metastasectomy (with negative margins). The overall risk of reoperation does not differ between surgical strategies nor does it differ based on margin status. This is explained by the finding that about half of the reoperations in the metastasectomy group were for deep infection, and the other half were for tumor recurrence; while the majority of reoperations in the intralesional treatment group and the stabilization only group were for tumor recurrence. Survival in our study was better after metastasectomy especially when negative margins were obtained, but these findings were confounded by the difference in metastatic load and our sample size was to small to demonstrate a difference in survival among patients with solitary bone metastasis only. Three previous studies addressed differences in survival based on resection type among patients with solitary renal cell bone metastasis and all demonstrated –in line with our study– a trend towards better survival in patients who undergo en bloc resection versus intralesional treatment, but small sample sizes fail to achieve sufficient power to demonstrate significance in all three.[36-38] A larger sample size, perhaps by combining the data from multiple institutions, is needed to determine the benefit in terms of survival for metastasectomy in patients with solitary or oligometastatic bone disease. In conclusion, based on our findings, patients with a relatively good life expectancy –more than one year– should undergo metastasectomy with negative margins to improve local tumor control in the long term at a non-significant additional risk for reoperation, and with a potential impact on survival.

Life expectancy for patients with bone metastasis is often estimated using prognostication algorithms. Numerous algorithms exist and can be categorized into: simple classic scoring systems, nomograms, and computer or application-based machine learning algorithms.[41-47] However, accuracy of currently existing algorithms in predicting survival is moderate and any improvement in performance would be clinically relevant. We assessed what factors were independently associated with survival among patients (n = 927) with long bone metastases undergoing surgery (Chapter 10). We identified two new factors associated with survival: comorbidity status and body mass index. These newly identified prognostic factors should be tested in future studies and incorporated in prognostication algorithms. Many other risk factors have been identified previously and most are confirmed in multiple subsequent studies, including: primary tumor type, performance status, presence of visceral and/or brain metastases, number of metastases, previous systemic therapy, age, hemoglobin level, sex, presence of a pathological fracture, the surgeons' estimate of survival, presence of pain.[41-47] More recently, emphasis has been put on further tumor characterization (e.g. specific gene mutations such as epidermal growth factor receptor for lung cancer) and biochemical variables (e.g. neutrophil count, alkaline phosphatase, C-reactive protein, lactate dehydrogenase, albumin, calcium, platelet level, bilirubin) in order to identify more prognostic factors.[48-50] Incorporating a multitude of prognostic factors in a survival algorithm increases model performance (i.e. more information leads to more precise and more accurate life expectancy estimates); however, this comes at the cost of increased model complexity and more burden to the person completing the algorithm due to the number of variables that need to be known and entered. Balancing model performance and simplicity is key for clinical use. Web-based applications such as pathfx.org[51] and optimal[52] help estimate life expectancy, but still need to be completed manually. Future lies in electronic medical records –perhaps connected on national or international level– that automatically provide survival estimates based on diagnostic and billing coding, tumor characteristics, biochemical variables, and natural language processing of physician notes. Ideally, these algorithms would continuously update through machine learning.[53] The latter is not only important for identifying subtle prognostic factors, but also to stay up-to-date with regards to the rapidly developing changes in systemic oncological therapy. Until then, our developed nomogram and web-based applications balance simplicity and stable model performance. Comparison and adjustment of prognostication tools would ideally be done in a new patient population to assess external validity and to compare accuracy of these algorithms.

Patients with bone metastasis are often chronically anemic. Blood loss during surgery for bone metastasis can worsen this anemia and often leads to blood transfusion. As the relationship between perioperative blood transfusions and adverse oncological outcomes (survival and tumor recurrence) has been demonstrated in resection of primary malignancies, the question arises how to manage perioperative anemia in patients undergoing surgery for bone metastasis. We therefore studied the impact of perioperative blood transfusions on survival among patients (n = 789) who undergo surgery for long bone metastases (Chapter 11). We found that perioperative blood transfusion in patients who undergo surgery for long bone metastases might negatively influence survival, although the effect is small. Other studies on surgery for spine metastasis demonstrated contradicting results; one found increased 12-months survival among patients who received 1 to 2 units of blood, while another study demonstrated no effect of exposure to blood transfusion nor a dose-response relationship.[54,55] We subsequently studied the effect of perioperative blood transfusion on infection within 90 days after surgical treatment for bone metastases.[54] We found no effect of exposure to blood transfusion, nor did we find a dose-response relationship (per unit of blood transfused) on the risk of developing a postoperative infection.[54] The negative impact of perioperative blood transfusion on postoperative complications, overall survival, and tumor recurrence has been demonstrated clearly in patients who undergo curative resection for colorectal cancer, but also in patients who undergo resection of colorectal liver metastases.[56-60] Given these findings, one needs to balance the risk of acute anemia versus the potential immunomodulation and its possible consequences imposed by allogeneic blood transfusions. Recommendations regarding cut-off points for transfusion cannot be given based on these studies. Future study could consider applying patient reported outcome measures such as quality of life to establish the impact of blood transfusions.

CONCLUSIONS

- For patients with proximal femoral metastasis, intramedullary nailing and endoprosthetic reconstruction are preferred over open reduction internal fixation (**Chapter 2 & 3**).
- Endoprosthetic reconstruction and intramedullary nailing for proximal femoral metastasis seem to be comparable in terms of overall risk for reoperation (**Chapter 2 & 3**).
- Implant-specific reasons for reoperation and their timing should be considered when deciding between endoprosthetic reconstruction and intramedullary nailing for proximal femoral metastasis (**Chapter 2 & 3**).
- The PROMIS Physical Function Cancer questionnaire is recommended for assessment of functional outcome in patients with lower extremity bone metastasis (**Chapter 4**).
- A clinical CT scan based algorithm can be useful for predicting occurrence of a pathological fracture through a femoral metastasis (**Chapter 5**).
- Endoprosthetic reconstruction, intramedullary nailing, and open reduction internal fixation seem to be reasonable options for treatment of humeral metastasis. Variation in indications and reporting of outcomes, and small and heterogeneous patient samples preclude direct comparison of surgical strategies (**Chapter 6**).

- The probability of undergoing reoperation increases considerably with longer survival in patients with humeral metastasis (**Chapter 7**).
- A prognostic survival score (modified Bauer score) could be useful for risk stratification of postoperative systemic complications in patients with femoral and humeral metastasis (**Chapter 2 & 7**).
- Subspecialty training of the surgeon, as well as tumor type, life expectancy, and anatomical location of a metastatic humeral lesions are important drivers of treatment variation (**Chapter 8**).
- Metastasectomy with negative margins for renal cell bone metastasis improves local tumor control at a comparable risk for reoperation, and with a potential impact on survival (**Chapter 9**).
- Comorbidity status and body mass index are two newly identified prognostic factors for survival in patients with long bone metastasis (**Chapter 10**).
- A nomogram is the preferred method for predicting survival probabilities in patients with long bone metastasis (**Chapter 10**).
- Perioperative allogeneic blood transfusions in patients with long bone metastasis are a potential modifiable risk factor as it might negatively affect survival; although the effect is small (**Chapter 11**).

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